REMARKS

Applicants have amended claim 14 to recite a method for determining the risk estimate of cancer in a subject, where the method includes detecting the presence or absence of a sulfotransferase nucleotide sequence variant that encodes a SULT1A1 polypeptide having a histidine at residue 213. Support for this amendment can be found in original claim 33 and in the specification at, for example, page 6, line 25 to page 7, line 6, and page 11, lines 7-12. New claim 37 depends from claim 14 and recites that the cancer is a hormone dependent cancer. Support for claim 37 can be found in original claim 14. The dependency of claims 15-17 and 34 has been amended to conform with the other claim amendments. Claim 33 has been canceled without prejudice. In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 14-17, 32, and 34-37.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 14-17 and 32-36 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner asserted that the specification does not teach that any of the disclosed polymorphisms of *SULT1A1*, *SULT1A2*, or *SULT1A3* has a defined correlation to any particular hormone dependent disease. The Examiner further asserted that although the specification discloses that a polymorphism at nucleotide 638 of *SULT1A1* results in a difference in activity, there is no showing that the difference in activity is correlated with an altered risk of developing a hormone dependent disease. Thus, the Examiner alleged that "it would take undue experimentation to determine how even the presence or absence of any one allele of even this particular polymorphism correlates with such risk as the correlation may be different for distinct diseases as well as for distinct causes of even the same disease and the number of factors involved is immense."

The specification enables one of ordinary skill in the art to practice the presently claimed invention, which relates to methods for determining the risk estimate of cancer in a subject by detecting a sulfotransferase nucleotide sequence variant encoding a SULT1A1 polypeptide with a histidine at residue 213. The SULT1A1 allozyme having a histidine at residue 213 is encoded by the *SULT1A1*2* allele, which contains a nucleotide variant at position 638 of the coding sequence. The specification indicates that subjects containing the *SULT1A1*2* allele may have a

greater likelihood of developing breast cancer. See, for example, the specification at page 11, lines 14-17. The specification also states that the allozyme encoded by the *SULT1A1*2* allele has a higher level of activity in patients with malignant hepatic disease than in patients with benign disease. See the specification at, for example, page 32, lines 3-10.

Vachon et al. ("*SULT1A1* and HRT-associated increases in mammographic breast density," presented at the 2002 American Association of Cancer Research meeting), Zheng et al. ((2001) *Cancer Epidemiology, Biomarkers & Prevention* 10:89-94), and Wu et al. ((2003) *Int. J. Cancer* 103:101-104) confirm that a SULT1A1 allozyme having a His at position 213 results in an increased risk for developing cancer. See references AQ, AR, and AS on the Supplemental Information Disclosure Statement enclosed herewith. Vachon et al. demonstrate that the presence of the *SULT1A1*2* allele is associated with increased mammographic percent density (PD) in women receiving hormone replacement therapy and undergoing screening mammograms. Both PD and HRT are known risk factors for breast cancer. The increase in PD was greatest in women with two *SULT1A1*2* alleles, although women with one wild type allele and one *SULT1A1*2* allele also exhibited increased PD after initiation of HRT (p-trend=0.04).

The Zheng et al. reference teaches that a SULT1A1 polypeptide having a histidine residue at position 213 is associated with increased risk of breast cancer. Similar to the studies of Vachon et al., the risk of breast cancer was elevated in women with one *SULT1A1 His* allele, and was further elevated in women with two *SULT1A1 His* alleles (p-trend = 0.027). In addition, the odds ratio (OR) for the homozygous genotype was statistically significant (OR = 1.8; P = 0.04).

The Wu et al. reference provides evidence that a *SULT1A1 His* allele is associated with esophageal cancer. Wu et al. found that a significantly higher percentage of subjects with esophageal cancer carried a *SULT1A1 His* allele than controls ($p < 0.0001$). After adjusting for other covariates such as age, education level, ethnicity, cigarette smoking, alcohol use, and areca chewing, subjects carrying a single *SULT1A1 His* allele were determined to have a 3.23-fold greater risk of developing esophageal cancer than study subjects having two *SULT1A1* alleles encoding a polypeptide with arginine at position 213.

Thus, the Vachon et al., Zheng et al., and Wu et al. references confirm that the presence of a nucleotide sequence variant encoding a SULT1A1 allozyme with a histidine residue at

position 213 is correlated with cancer. Therefore, based on the specification and further in view of knowledge in the art, one of skill in the art could practice the presently claimed method without undue experimentation. In view of the above remarks, the Examiner is respectfully requested to withdraw the rejection of claims 14-17, 32, and 34-36 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendments. Applicant submits that claims 14-17, 32, and 34-37 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

The paragraph beginning at page 1, line 4, has been amended as follows:

This application is a divisional of U.S. Serial No. 09/167,681, filed October 7, 1998, now U.S. Patent No. 6,265,561.

In the claims:

Claim 33 has been canceled.

Claims 14-17 and 34 have been amended as follows:

14. (Amended) A method for determining the risk estimate of [a hormone dependent disease] cancer in a subject, said method comprising detecting the presence or absence of a sulfotransferase nucleotide sequence variant in said patient, wherein said sulfotransferase nucleotide sequence variant encodes a SULT1A1 polypeptide having a histidine at residue 213, and determining said risk estimate based, at least in part, on the presence or absence of said variant in said subject.

15. (Amended) The method of claim [14] 37, wherein said hormone dependent [disease] cancer is breast cancer.

16. (Amended) The method of claim [14] 37, wherein said hormone dependent [disease] cancer is prostate cancer.

17. (Amended) The method of claim [14] 37, wherein said hormone dependent [disease] cancer is ovarian cancer.

34. (Amended) The method of claim [15] 14, wherein said sulfotransferase nucleotide sequence variant comprises the SULT1A1*2 allele.